Journal of Multivariate Analysis 100 (2009) 301–308

Contents lists available at ScienceDirect

Journal of Multivariate Analysis

journal homepage: www.elsevier.com/locate/jmva

Exact inference on contrasts in means of intraclass correlation models with missing responses

Mi-Xia Wu[a,b,∗], Kai F. Yu[b], Aiyi Liu[b]

[a] College of Applied Sciences, Beijing University of Technology, Beijing 100022, China

[b] Biometry and Mathematical Statistics Branch, Division of Epidemiology, Statistics and Prevention Research, National Institute of Child Health and Human Development, NIH/DHHS, 6100 Executive Boulevard, Rockville, MD 20852, USA

ARTICLE INFO

Article history:
Received 15 March 2007
Available online 8 May 2008

AMS 2000 subject classifications:
primary 62H15
secondary 62H12

Keywords:
Contrast
Exact test
Intraclass correlation model
Linear mixed model
Simultaneous confidence intervals

ABSTRACT

Intraclass correlation models with missing data at random are considered. With a properly reduced model, a general method, which allows repeated observations with missing data in a non-monotone pattern, is proposed to construct exact test statistics and simultaneous confidence intervals for linear contrasts in the means. Simulation results are given to compare exact and asymptotic simultaneous confidence intervals. A real example is provided for the illustration of the proposed method.

Published by Elsevier Inc.

1. Introduction

Intraclass correlation models are popular choices to analyze data from block designs, or cluster sampling, or longitudinal studies with an individual random effect [2,9]. Here we deal with such studies in which the repeated observations are missing at random and the non-missing observations satisfy the two-component mixed linear model

$$x_{ij} = \mu_i + \alpha_j + \varepsilon_{ij}, \quad i \in O_j = \{j_1, \ldots, j_{p_j}\}, j = 1, \ldots, n, \tag{1}$$

where μ_i is the mean value of the ith observation, α_j is the random effect of the jth subject, $1 \le j_1 < \cdots < j_{p_j} \le p$. Here p, often pre-specified in the study design, is the number of repeated observations for each subject, p_j is the number of available observations from the jth subject, α_j and ε_{ij} are assumed to be independent and normally distributed with mean 0 and variances σ_α^2 and σ_ε^2, respectively. Denote $\mathbf{x}_j = (x_{j_1 j}, \ldots, x_{j_{p_j} j})'$, $\mathbf{u}_j = (\mu_{j_1}, \ldots, \mu_{j_{p_j}})'$. It is clear from the above assumption that $\mathbf{x}_1, \ldots, \mathbf{x}_n$ are independent, $E(\mathbf{x}_j) = \mathbf{u}_j$ and

$$\mathrm{Cov}(\mathbf{x}_j) = \Sigma_j = \sigma^2 \left((1-\rho) I_{p_j} + \rho J_{p_j} \right), \tag{2}$$

where $\sigma^2 = \sigma_\alpha^2 + \sigma_\varepsilon^2$, $\rho = \sigma_\alpha^2/\sigma^2$, I_{p_j} is the $p_j \times p_j$ identity matrix, $\mathbf{1}_{p_j} = (1, \ldots, 1)'$, and $J_{p_j} = \mathbf{1}_{p_j}\mathbf{1}_{p_j}'$.

Our interest lies in the inference on contrasts of the mean vector $\mathbf{u} = (\mu_1, \mu_2, \ldots, \mu_p)'$ under model (1). For the case of all $p_j = p$ (balanced data), a number of efficient inference procedures exist on hypothesis testing and estimation of the

∗ Corresponding author at: Biometry and Mathematical Statistics Branch, Division of Epidemiology, Statistics and Prevention Research, National Institute of Child Health and Human Development, NIH/DHHS, 6100 Executive Boulevard, Rockville, MD 20852, USA.

E-mail address: wumixia@gmail.com (M.-X. Wu).

0047-259X/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.jmva.2008.05.002

parameters in model (1). Indeed, one can find the uniformly minimum variance unbiased (UMVU) estimators, most powerful unbiased tests and exact simultaneous confidence intervals for all contrasts in means [5,1]. However, when missing data occur, these optimal properties do not hold, and we cannot even construct exact inference on contrasts in means by the analysis of variance (ANOVA) method or the likelihood method. In this case, the asymptotic inference on parameters of intraclass correlation model based on likelihood method are usually considered in the literature. Srivastava and Carter [7] discussed the maximum likelihood (ML) method for the intraclass correlation model with missing data. Based on their asymptotic theories, Seo and Srivastava [6] gave the asymptotic simultaneous confidence interval for all contrasts in means. Note that the results of asymptotic inference are usually affected by sample size and missing pattern. Moreover, the ML method requires extensive numerical iterative computations since there does not exist explicit ML estimation of $(\mathbf{u}, \sigma_\alpha^2, \sigma_\varepsilon^2)$ under model (1) with missing data; see [8]. Thus simple and efficient exact tests and estimators are desirable in practice. By a certain transformation, Seo and Srivastava [6] gave an exact test statistic for the equality of the means and simultaneous confidence intervals for all contrasts in the means when the missing observations follow the monotone-type missingness, i.e. $O_j = \{1, \ldots, p_j\}$ in model (1); see [4] for definitions of various types of missingness. However, when the missing type is non-monotone, the problem of finding exact tests and estimation of contrasts in means is yet to be solved. The main difficulty lies in giving the expression of estimator for the parameter of interest under a transformation model when missing data occur. This paper considers the exact inference on all contrasts of means under model (1) when the missing observations do not follow a monotone pattern. A simple method is given to construct exact confidence intervals and exact test statistics for contrasts in means. By defining index matrix of contrasts in the means for each subject, Section 2 introduces a reduced model. Based on this reduced model, Sections 3 and 4 provide a simple estimator, exact test statistic, and simultaneous confidence intervals for all contrasts in means. Finally, some simulation results and a real example are presented in Sections 5 and 6, respectively.

2. Reduced model for contrasts in means

In this paper, contrasts in the mean vector $\mathbf{u} = (\mu_1, \ldots, \mu_p)'$ are of primary interest. Denote $\xi_i = \mu_i - \mu_{i+1}$ and $\xi = (\xi_1, \ldots, \xi_{p-1})'$. It is easy to see that any contrast $\mathbf{a}'\mathbf{u}$ can be transformed as a linear function of ξ, where $a = (a_1, \ldots, a_p)'$ is a non-null vector such that $\mathbf{a}'\mathbf{1}_p = 0$. In fact, let $b_i = \sum_{j=1}^{i} a_j$ and $\mathbf{b} = (b_1, \ldots, b_{p-1})'$. Then

$$\mathbf{a}'\mathbf{u} = \sum_{i=1}^{p-1} b_i \xi_i = \mathbf{b}'\xi. \tag{3}$$

Thus statistical inference on all contrasts in means can be reduced to the corresponding inference on the new parameter vector $\boldsymbol{\xi}$, hereafter referred to as the contrast parameter.

We consider the transformation $\mathbf{y}_j = C_{p_j}\mathbf{x}_j$, where

$$C_{p_j} = \begin{bmatrix} 1 & -1 & 0 & \cdots & \cdots & 0 \\ 0 & 1 & -1 & 0 & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & \cdots & \cdots & \cdots & 1 & -1 \end{bmatrix}_{(p_j-1)\times p_j} \tag{4}$$

for $p_j > 1$ and $C_1 = 0$. Clearly, $\mathbf{y}_j = 0$ when $p_j = 1$. Without loss of generality, we assume that $p_j \geq 2$ for $j \leq n_0 (\leq n)$ and $p_j \leq 1$ otherwise. Note that

$$E(\mathbf{y}_j) = C_{p_j}\mathbf{u}_j = (\mu_{j_1} - \mu_{j_2}, \ldots, \mu_{j_{p_j-1}} - \mu_{j_{p_j}})', \tag{5}$$

$$\mu_i - \mu_j = \sum_{l=i}^{j-1} (\mu_l - \mu_{l+1}) = \sum_{l=i}^{j-1} \xi_l, \quad 1 \leq i < j \leq p.$$

Hence there exists a $(p_j - 1) \times (p - 1)$ matrix B_j such that

$$C_{p_j}\mathbf{u}_j = B_j\xi.$$

In fact, B_j can be defined as follows.

Definition 1. $B_j = (b_{kl}^{(j)})$,

$$b_{kl}^{(j)} = \begin{cases} 1, & \text{if } j_k \leq l \leq j_{k+1} - 1, \\ 0, & \text{otherwise,} \end{cases} \tag{6}$$

$k = 1, \ldots, p_j - 1$, $l = 1, \ldots, p - 1$. B_j is called the index matrix of contrasts in the means for the jth subject.

Thus model (1) can be transformed into

$$\mathbf{y}_j = B_j\xi + e_j, \qquad \mathrm{Cov}(e_j) = \sigma_\varepsilon^2 G_{p_j} \quad j = 1, \ldots, n_0, \tag{7}$$

where $G_{p_j} = C_{p_j}C'_{p_j} > 0$. The reduced model (7) is called the model for contrast parameter ξ.

Clearly, the reduced model is a linear regression model only on the parameter of interest ξ and variance parameter σ_ε^2. Thus the complicated issue of estimating ρ and the mean vector with unbalanced data is avoided.

3. Estimation and exact test statistics

Note that B_j is of full rank. Thus ξ is estimable under the reduced model (7). From the well known least squares theory (e.g. [10]), the reduced model (7) yields the unbiased estimator of $(\xi, \sigma_\varepsilon^2)$:

$$\begin{cases} \hat{\xi} = \left(\sum_{j=1}^{n_0} B_j' G_{p_j}^{-1} B_j\right)^{-1} \sum_{j=1}^{n_0} B_j' G_{p_j}^{-1} \mathbf{y}_j, \\ \hat{\sigma}_\varepsilon^2 = \sum_{j=1}^{n_0} \left(\mathbf{y}_j - B_j\hat{\xi}\right)' G_{p_j}^{-1} \left(\mathbf{y}_j - B_j\hat{\xi}\right) \Big/ f, \end{cases} \tag{8}$$

and the following theorem.

Theorem 1. *$\hat{\xi} \sim N(C_p\mathbf{u}, \sigma_\varepsilon^2 \Sigma_{\hat{\xi}})$, $f\hat{\sigma}_\varepsilon^2/\sigma_\varepsilon^2 \sim \chi_f^2$, $\hat{\xi}$ and $\hat{\sigma}_\varepsilon^2$ are independent, where $f = \sum_{j=1}^{n_0} p_j - n_0 - p + 1$, $\Sigma_{\hat{\xi}} = (\sum_{j=1}^{n_0} B_j' G_{p_j}^{-1} B_j)^{-1}$.*

By Theorem 1, we can construct an exact test statistic for the null hypothesis $H_0 : B\xi = \delta_0$ for any $m \times (p-1)$ matrix B and $m \times 1$ vector δ_0. The test statistic is given by

$$F_0(B, \delta_0) = (B\hat{\xi} - \delta_0)'(B'\Sigma_{\hat{\xi}}B)^{-1}(B\hat{\xi} - \delta_0)/r\hat{\sigma}_\varepsilon^2, \tag{9}$$

where $r = \operatorname{rank}(B)$. Clearly, $F_0(B, \delta_0)$ follows an F-distribution with degrees of freedom r and f under H_0.

In particular, for the null hypothesis $H_0 : \mu_1 = \cdots = \mu_p$, that is, $H_0 : \xi = 0$, we have a test statistic

$$F_0(I_{p-1}, 0) = \hat{\xi}'\Sigma_{\hat{\xi}}^{-1}\hat{\xi}/(p-1)\hat{\sigma}_\varepsilon^2, \tag{10}$$

which has an F-distribution with degrees of freedom $p-1$ and f under the null hypothesis $H_0 : \xi = 0$.

Noting that under the null hypothesis $H_0 : \mu_1 = \cdots = \mu_p$,

$$\tilde{y}_j = (C_{p_j}C_{p_j}')^{1/2}C_{p_j}x_j \sim N(0, \sigma_\varepsilon^2 I_{p_j-1}), \quad j = 1, \ldots, n_0,$$

Seo and Srivastava [6] obtained two exact test statistics for testing H_0. Let y_j be a $(p-1) \times 1$ vector with element $y_{lj} = \tilde{y}_{ij}$ if $l = j_{i+1} - 1$, and $y_{lj} = 0$, if otherwise, $i = 1, \ldots, p_j - 1$, where j_i is defined in (1). Then the first test statistic in [6] can be written as

$$F_{S\&S1} = \frac{\sum_{i=1}^{p-1} n_i^* \bar{y}_{i.}/(p-1)}{\hat{\gamma}^2},$$

where $\bar{y}_{i.} = \sum_{j=1}^{n_0} y_{ij}/n_i^*$, $\hat{\gamma}^2 = \sum_{i=1}^{p-1}\{\sum_{j=1}^{n_0}(y_{ij} - \bar{y}_{i.})^2 - (n_0 - n_i^*)\bar{y}_{i.}^2\}/f_1$, $f_1 = \sum_{i=1}^{p-1} n_i^* - (p-1)$, and n_i^* is the number of non-zero elements in the set $\{y_{i1}, \ldots, y_{in_0}\}$.

Without loss of generality, we assume that $p_1 \le p_2 \le \cdots \le p_{n_0}$. Rearranging y_j as $(\tilde{y}_{1j}, \ldots, \tilde{y}_{(p_j-1)j}, 0, \ldots, 0)$, the second test statistic by [6] is then

$$F_{S\&S2} = \frac{\sum_{i=1}^{p-1} \tilde{n}_i \bar{y}_{i.}/(p-1)}{\bar{\gamma}^2},$$

where $\bar{y}_{i.} = \sum_{j=1}^{\tilde{n}_i} y_{ij}/\tilde{n}_i$, $\bar{\gamma}^2 = \sum_{i=1}^{p-1}\sum_{j=1}^{\tilde{n}_i}(y_{ij} - \bar{y}_{i.})^2/f_2$, $f_2 = \sum_{i=1}^{p-1}\tilde{n}_i - (p-1)$, and $\tilde{n}_i$ is the number of non-zero elements in the set $\{y_{i1}, \ldots, y_{in_0}\}$.

Clearly, $f_1 = f_2 = f$. Furthermore, $F_{S\&S1}$ and $F_{S\&S2}$ have the same null distribution as $F_0(I_{p-1}, 0)$ in (10). However, the distributions of $F_{S\&S1}$ and $F_{S\&S2}$ become very complicated under the alternative hypotheses (i.e. when the means are not equal). A comparison of the three test statistics is presented in Section 5.

Another special case of (9) is $B = \mathbf{b}$, in which the test statistic $F_0(\mathbf{b}, \delta_0)$ is usually replaced by the t-statistic

$$t_0 = (\mathbf{b}'\hat{\xi} - \delta_0)/\hat{\sigma}_\varepsilon\sqrt{\mathbf{b}'\Sigma_{\hat{\xi}}\mathbf{b}}, \tag{11}$$

which has a t-distribution with f degrees of freedom under $H_0 : \mathbf{b}'\xi = \delta_0$.

Alternative expressions can be obtained to relax the complexity of computation of (8) which includes computing the inverse matrix for each G_{p_j}. Indeed, we have

$$\begin{cases} \hat{\xi} = C_p\hat{\eta}, \\ \hat{\sigma}_\varepsilon^2 = \sum_{j=1}^{n_0}\sum_{i=1}^{p_j}\left(x_{j_ij} - \bar{x}_{.j} - \hat{\eta}_{j_i} + \bar{\hat{\eta}}_{.j}\right)^2 \Big/ f, \end{cases} \tag{12}$$

where $\hat{\boldsymbol{\eta}} = (\hat{\eta}_1, \ldots, \hat{\eta}_p)' = (V - M)^{+}\mathbf{z}$, $\bar{x}_{.j} = \sum_{i=1}^{p_j} \bar{x}_{j_i j}/p_j$ and $\bar{\hat{\eta}}_{.j} = \sum_{i=1}^{p_j} \hat{\eta}_{j_i}/p_j$. Here $(\cdot)^{+}$ denotes the Moore–Penrose generalized inverse of matrix $(\cdot)$, $\mathbf{z} = (z_1, \ldots, z_p)'$, $V = \mathrm{diag}(n_i)$ and $M = (m_{kl})$ with elements

$$z_i = \sum_{j=1}^{n_0} (x_{ij} - \bar{x}_{.j})\delta_{ij}, \qquad n_i = \sum_{j=1}^{n_0} \delta_{ij}, \qquad m_{kl} = \sum_{j=1}^{n_0} \delta_{kj}\delta_{lj}/p_j,$$

$1 \le i, k, l \le p$, where

$$\delta_{ij} = \begin{cases} 1, & \text{if } i \in O_j, \\ 0, & \text{otherwise.} \end{cases}$$

Moreover, we can simplify the computations of test statistics (9)–(11) by replacing $\Sigma_{\hat{\xi}}$ with

$$\Sigma_{\hat{\xi}} = C_p(V - M)^{+}C_p'. \tag{13}$$

For the proof of (12) and (13) see the Appendix.

Clearly, when all $p_j = p$, expressions (12) are tantamount to

$$\begin{cases} \hat{\xi} = C_p\bar{\mathbf{x}}, \\ \hat{\sigma}_\varepsilon^2 = \sum_{j=1}^{n}\sum_{i=1}^{p} \left(x_{ij} - \bar{x}_{.j} - \bar{x}_{i.} + \bar{x}_{..}\right)^2 / (n-1)(p-1), \end{cases}$$

where $\bar{\mathbf{x}} = \sum_{j=1}^{n} \mathbf{x}_j/n$, $\bar{x}_{i.} = \sum_{j=1}^{n} x_{ij}/n$ and $\bar{x}_{..} = \sum_{i=1}^{p}\sum_{j=1}^{n} x_{ij}/pn$. Thus $(\hat{\xi}, \hat{\sigma}_\varepsilon^2)$ is the UMVU estimator of $(C_p\mathbf{u}, \sigma_\varepsilon^2)$ and the test based on test statistic (9) is the most powerful unbiased test when there are no missing observations, see [5].

4. Simultaneous confidence intervals

In this section, we consider simultaneous confidence intervals of contrasts $\mathbf{a}'\mathbf{u}$ for any non-null vector $\mathbf{a} = (a_1, \ldots, a_p)'$ such that $\mathbf{a}'\mathbf{1} = 0$. Using (10) and (11) we have the following exact confidence intervals.

(i) The Scheffè type of simultaneous confidence intervals for all contrasts are given by

$$\mathbf{a}'\mathbf{u} \in \left[\mathbf{b}'\hat{\xi} \pm \hat{\sigma}_\varepsilon\sqrt{(p-1)F_{p-1,f,\alpha}\mathbf{b}'\Sigma_{\hat{\xi}}\mathbf{b}}\right], \tag{14}$$

where $\mathbf{b}$ is defined in (3), $F_{p-1,f,\alpha}$ is the upper $100\alpha\%$ quantile of an F-distribution with degrees of freedom $p-1$ and f.

(ii) The Bonferroni type of simultaneous confidence intervals for k contrasts are given by

$$\mathbf{a}_i'\mathbf{u} \in \left[\mathbf{b}_i'\hat{\xi} \pm \hat{\sigma}_\varepsilon t_{f,\frac{\alpha}{2k}}\sqrt{\mathbf{b}_i'\Sigma_{\hat{\xi}}\mathbf{b}_i}\right], \quad i = 1, \ldots, k, \tag{15}$$

where $\mathbf{b}_i$ is defined similarly as (3), and $t_{f,\alpha/(2k)}$ is the upper $100\alpha/(2k)\%$ quantile of a t-distribution with f degrees of freedom.

Note that if $t_{f,\frac{\alpha}{2k}} > \sqrt{(p-1)F_{p-1,f,\alpha}}$, then the Bonferroni type simultaneous confidence intervals can be replaced by the Scheffè type of simultaneous confidence intervals.

(iii) Let $k = 1$ in (15). Then the exact confidence interval for a contrast is given by

$$\mathbf{a}'\mathbf{u} \in \left[\mathbf{b}'\hat{\xi} \pm \hat{\sigma}_\varepsilon t_{f,\frac{\alpha}{2}}\sqrt{\mathbf{b}'\Sigma_{\hat{\xi}}\mathbf{b}}\right]. \tag{16}$$

It follows from the asymptotic theory of maximum likelihood estimator (MLE) that

$$T^2 = (C_p\hat{\mathbf{u}})'\left[C_pW(\hat{\sigma}^2, \hat{\rho})C_p'\right]^{-1} C_p\hat{\mathbf{u}} \tag{17}$$

has asymptotically χ^2 distribution with $p-1$ degrees of freedom. Using this, Seo and Srivastava [6] gave asymptotic simultaneous confidence intervals for linear contrasts $\mathbf{a}'\mathbf{u}$ by

$$\mathbf{a}'\mathbf{u} \in \left[\mathbf{a}'\hat{\mathbf{u}} \pm \sqrt{\chi^2_{p-1,\alpha}\mathbf{a}'C_pW(\hat{\sigma}^2, \hat{\rho})C_p'\mathbf{a}}\right], \tag{18}$$

where $(\hat{\mathbf{u}}, \hat{\sigma}^2, \hat{\rho})$ are MLE of $(\mathbf{u}, \sigma^2, \rho)$ in model (1),

$$W(\sigma^2, \rho) = \left[\sum_{j=1}^{n} D_j'\Sigma_j^{-1}D_j\right]^{-1}.$$

Here D_j is a $p_j \times p$ matrix with the (l, j_l)-element being one for $l = 1, \ldots, p_j$ and zero elsewhere.

To compare the exact and asymptotic simultaneous confidence intervals, it is noticed that the former always ensures the coverage probability to be equal to the specified confidence level $1-\alpha$. However, the coverage probabilities of the latter is affected by the sample size and missing type. In fact, the coverage probabilities are usually much smaller than the nominal confidence level $1-\alpha$ when the sample size is small and data are severely missing; see the simulation results below.

Table 1
Estimated coverage probabilities (runs:10000)

ρ	Type I		Type II	
	Scheffé	Asymptotic	Scheffé	Asymptotic
$n = 20$				
0.1	0.9483	0.9189	0.9482	0.9036
0.5		0.9214		0.9052
0.9		0.9227		0.9023
$n = 40$				
0.1	0.9507	0.9408	0.9502	0.9205
0.5		0.9403		0.9187
0.9		0.9399		0.9141

Nominal confidence level $1 - \alpha = 0.95$.

5. Simulation

In this section, firstly, we compare via the Monte Carlo simulation the coverage probabilities and lengths of exact simultaneous confidence intervals (Scheffè type) with that of asymptotic simultaneous confidence intervals. Let $p = 3$, $\mu = (3, 3, 5)'$, $\sigma_\varepsilon^2 = \sigma^2(1 - \rho) = 1$ and $\alpha = 0.05$. Results are displayed for three different choices (0.1, 0.5, 0.9) of ρ, two different missing types (I, II), with 10 000 replicates and $n = 20, 40$ subjects per replicate generated in each case. Here the two missing types are, respectively,

Type I: $\{11(0), 3(1), 3(2), 3(3)\}$,

Type II: $\{2(0), 3(1), 9(2), 4(3), 2(2, 3)\}$,

where $k(i) = k(i, i)$, and $k(i, j)$ means that there are $k \cdot (n/20)$ subjects missing in only the ith and jth observations, $i, j = 0, 1, 2, 3$. Clearly, the data set in Type II is missing more severely than that in Type I.

Critical values of $F_{p-1,f,\alpha}$ in the Scheffè type of simultaneous confidence intervals for $n = 20, 40$ are respectively given by $F_{2,29,0.05} = 3.33$, $F_{2,60,0.05} = 3.15$ under Type I; $F_{2,18,0.05} = 3.55$, $F_{2,38,0.05} = 3.24$ under Type II. Critical values of $\chi^2_{p-1,\alpha}$ in the asymptotic simultaneous confidence intervals are $\chi^2_{2,0.05} = 5.99$ for all cases of $n = 20, 40$ and missing types I and II. The corresponding estimated coverage probabilities for the three choices (0.1, 0.5, 0.9) of ρ are given in Table 1. The table shows that the approximation of asymptotic simultaneous confidence intervals is not satisfactory with small sample size and the coverage probabilities are considerably below the specified confidence level as the data are severely missing. One the other hand, our proposed exact confidence intervals guarantee the correct coverage probability, but at the cost of having longer lengths. When the sample size is relatively small, one may wish to make a compromise between the coverage probability and the length of the confidence intervals.

We further compare the widths of the Scheffè type simultaneous confidence intervals for $\mu_1 - \mu_2, \mu_1 - \mu_3, \mu_2 - \mu_3, 2\mu_1 - \mu_2 - \mu_3, \mu_1 - 2\mu_2 + \mu_3$ with that of asymptotic simultaneous confidence intervals by averaging the lengths of the simultaneous confidence intervals from the 10 000 replicates. Table 2 shows that the differences in lengths between the two methods are larger with missing Type II than that with missing type I.

Therefore, with small sample size and severely missing data, the exact method is more appealing than the asymptotic method.

Table 3 compares the power of our proposed test with the two exact tests by [6] for testing $H_0 : \mu_1 = \cdots = \mu_p$, all with the same level of significance of 0.05. Since all three test statistics are independent of ρ in model (1), we set $\rho = 0.1$. The table shows that in most cases the power of the test based on $F_0(I_{p-1}, 0)$ is the highest for unequal means, and the power of $F_{S\&S2}$ is the lowest. Moreover, the power of $F_{S\&S1}$ and $F_{S\&S2}$ is substantially adversely affected by the order of the μ_is. Though performing almost equally well if the values of $\{\mu_i\}$ are in monotonic order, the two exact tests $F_{S\&S1}$ and $F_{S\&S2}$ have much lower power under other alternatives than the proposed test in the present paper.

6. An example

In this section, we shall discuss a set of data from the Calcium for Preeclampsia Prevention (CPEP) Study [3] to illustrate the method developed in this paper. In this study, blood samples were collected during the trial from the study participants at various gestational age, and soluble fms-like tyrosine kinase 1 (sFlt1) levels (pg/ml) were assayed from the blood samples of a subgroup of study participants, at six intervals of gestational age, 8–20, 21–24, 25–28, 29–32, 33–36, and 37–39 weeks. One interest of the trial is to investigate how the sFlt1 levels change over gestational age, especially among women who have preeclampsia.

During the trial 149 women were diagnosed as having preeclampsia. Among these, there are 22 women with only one observation each, the remaining 127 with two to four observations each during the six intervals of gestational age. Here $p = 6, n_0 = 127, n = 149$. Since the sFlt1 value is large, we consider the observations after logarithmic transformation.

Table 2
Average widths of simultaneous confidence intervals (runs: 10000)

$\mathbf{a}'$	Type	Scheffè	Asymptotic		
		(any ρ)	$\rho = 0.1$	$\rho = 0.5$	$\rho = 0.9$
$n = 20$					
(1, −1, 0)	I	1.840	1.606	1.661	1.684
	II	2.580	1.925	2.095	2.216
(1, 0, −1)	I	1.840	1.606	1.661	1.684
	II	2.094	1.661	1.756	1.808
(0, 1, −1)	I	1.840	1.606	1.661	1.684
	II	2.666	1.997	2.175	2.293
(−2, 1, 1)	I	3.188	2.782	2.876	2.916
	II	3.870	2.990	3.197	3.332
(1, −2, 1)	I	3.188	2.782	2.876	2.916
	II	4.811	3.553	3.893	4.131
$n = 40$					
(1, −1, 0)	I	1.270	1.167	1.199	1.215
	II	1.766	1.406	1.526	1.611
(1, 0, −1)	I	1.270	1.167	1.199	1.215
	II	1.543	1.215	1.277	1.315
(0, 1, −1)	I	1.270	1.167	1.199	1.215
	II	1.835	1.459	1.585	1.668
(−2, 1, 1)	I	2.199	2.021	2.076	2.104
	II	2.763	2.186	2.326	2.424
(1, −2, 1)	I	2.199	2.021	2.076	2.104
	II	3.255	2.596	2.837	3.005

Table 3
The powers of three tests for equality of means (runs: 5000)

Type	n	Test statistic	μ			
			(3 2 3)	(3 3 4)	(3 4 3)	(4 3 3)
I	20	$F_0(I_{p-1}, 0)$	0.7812	0.794	0.7864	0.7806
		$F_{S\&S1}$	0.236	0.8092	0.2502	0.7826
		$F_{S\&S2}$	0.0908	0.7784	0.0964	0.7546
	40	$F_0(I_{p-1}, 0)$	0.9844	0.987	0.9864	0.9808
		$F_{S\&S1}$	0.5734	0.9836	0.579	0.9752
		$F_{S\&S2}$	0.1484	0.9712	0.154	0.969
II	20	$F_0(I_{p-1}, 0)$	0.4224	0.5974	0.4258	0.6232
		$F_{S\&S1}$	0.1916	0.5948	0.1948	0.5466
		$F_{S\&S2}$	0.0364	0.4964	0.0354	0.5388
	40	$F_0(I_{p-1}, 0)$	0.7702	0.9264	0.7702	0.9324
		$F_{S\&S1}$	0.4038	0.9202	0.408	0.873
		$F_{S\&S2}$	0.0564	0.8302	0.0512	0.876

Nominal insignificant level $1 - \alpha = 0.95$.

Denote by μ_i the mean level of ln sFlt1 in the ith gestational age interval, $i = 1, \ldots, 6$. By Calculating (12) and (13), we obtain $\hat{\xi} = (-0.248, 0.074, -0.187, -0.853, -0.278)'$, $\hat{\sigma}_\varepsilon^2 = 0.196$,

$$\Sigma_{\hat{\xi}} = \begin{bmatrix} 0.205 & -0.202 & 0.005 & -0.001 & -0.004 \\ -0.202 & 0.218 & -0.021 & 0.006 & 0.002 \\ 0.007 & -0.02 & 0.104 & -0.090 & 0.013 \\ -0.003 & 0.008 & -0.090 & 0.102 & -0.030 \\ -0.004 & 0.002 & 0.013 & -0.030 & 0.128 \end{bmatrix},$$

and the value of test statistic in (10), $F_0 = \hat{\xi}'\Sigma_{\hat{\xi}}^{-1}\hat{\xi}/5\hat{\sigma}_\varepsilon^2 = 87.64 > F_{5,207,0.001}$. Therefore, the hypothesis $H_0 : \mu_1 = \mu_2 = \cdots = \mu_6$ is rejected. Using the Scheffé type of simultaneous confidence intervals and the asymptotic simultaneous confidence intervals in (14) and (18), simultaneous confidence intervals for $\mu_i - \mu_j$, $1 \le i < j \le 6$ with $1 - \alpha = 0.95$ are given in Table 4.

From Table 4, it may be noted that the Scheffé type of simultaneous confidence intervals are slightly longer than the asymptotic simultaneous confidence intervals. Both simultaneous confidence intervals can be adopted. Note that the data are severely missing in that, among these 149 women with preeclampsia, no women have more than four observations during the six intervals of gestational age. Here we recommend the Scheffé type of simultaneous confidence intervals.

Table 4
95% simultaneous confidence intervals

$\mu_i - \mu_j$	Scheffé type ($n_0 = 127$)	Asymptotic ($n = 149$)
$\mu_1 - \mu_2$	$[-0.248 \pm 0.675]$	$[-0.277 \pm 0.601]$
$\mu_1 - \mu_3$	$[-0.174 \pm 0.211]$	$[-0.167 \pm 0.197]$
$\mu_1 - \mu_4$	$[-0.360 \pm 0.450]$	$[-0.372 \pm 0.392]$
$\mu_1 - \mu_5$	$[-1.213 \pm 0.230]$	$[-1.200 \pm 0.216]$
$\mu_1 - \mu_6$	$[-1.491 \pm 0.504]$	$[-1.404 \pm 0.457]$
$\mu_2 - \mu_3$	$[0.074 \pm 0.696]$	$[0.110 \pm 0.613]$
$\mu_2 - \mu_4$	$[-0.113 \pm 0.789]$	$[-0.094 \pm 0.695]$
$\mu_2 - \mu_5$	$[-0.966 \pm 0.691]$	$[-0.922 \pm 0.614]$
$\mu_2 - \mu_6$	$[-1.244 \pm 0.835]$	$[-1.127 \pm 0.740]$
$\mu_3 - \mu_4$	$[-0.187 \pm 0.480]$	$[-0.204 \pm 0.411]$
$\mu_3 - \mu_5$	$[-1.039 \pm 0.240]$	$[-1.033 \pm 0.227]$
$\mu_3 - \mu_6$	$[-1.317 \pm 0.517]$	$[-1.237 \pm 0.466]$
$\mu_4 - \mu_5$	$[-0.853 \pm 0.475]$	$[-0.828 \pm 0.413]$
$\mu_4 - \mu_6$	$[-1.131 \pm 0.613]$	$[-1.033 \pm 0.559]$
$\mu_5 - \mu_6$	$[-0.278 \pm 0.533]$	$[-0.205 \pm 0.479]$

Acknowledgments

This research was supported by the Intramural Research Program of the National Institute of Child Health and Human Development, National Institutes of Health. Wu's research was also partially supported by Funding Project for Academic Human Resources Development in Institutions of Higher Learning Under the Jurisdiction of Beijing Municipality PHR(IHLB) and National Natural Science Foundation of China (NSFC). The authors thank the Calcium for Preeclampsia Prevention (CPEP) Research Study Group for providing them with the soluble fms-like tyrosine kinase 1 (sFlt1) data. They are also grateful to the two referees for their valuable suggestions which considerably improved the paper.

Appendix

Proofs of (12) and (13). Let D_j be a $p_j \times p$ matrix with the (l, j_l)-element being one for $l = 1, \ldots, p_j$ and zero elsewhere. Then $\mathbf{u}_j = D_j\mathbf{u}$. Combining this with the fact that $B_j\xi = C_{p_j}\mathbf{u}_j$ and $\xi = C_p\mathbf{u}$, we have $B_jC_p\mathbf{u} = C_{p_j}D_j\mathbf{u}$ for any $\mathbf{u} \in R^p$. Thus

$$B_jC_p = C_{p_j}D_j,$$

yielding

$$B_j = C_{p_j}D_jC_p'(C_pC_p')^{-1} \tag{A.1}$$

since C_p is of full (row) rank. Furthermore, it is easy to verify that

$$C_{p_j}'G_{p_j}^{-1}C_{p_j} = I_{p_j} - \bar{J}_{p_j}, \qquad \mathbf{1}_p'D_j'(I_{p_j} - \bar{J}_{p_j}) = 0,$$
$$\sum_{j=1}^{n_0} D_j'D_j = \mathrm{diag}(n_i) = V, \qquad \sum_{j=1}^{n_0} D_j'\bar{J}_{p_j}D_j = (m_{kl}) = M,$$

where $\bar{J}_{p_j} = J_{p_j}/p_j$. Hence we have

$$\begin{aligned}
\Sigma_{\hat{\xi}} &= \left(\sum_{j=1}^{n_0} B_j'G_{p_j}^{-1}B_j\right)^{-1} \\
&= C_pC_p'\left(C_p(V-M)C_p'\right)^{-1}C_pC_p' \\
&= C_pA\left(A'(V-M)A\right)^{+}A'C_p' \\
&= C_p(V-M)^{+}C_p
\end{aligned} \tag{A.2}$$

where $A = (C_p', \mathbf{1}_p)$. This proves (13). The last equality makes use of the invertibility of matrix A. Moreover, because

$$\sum_{j=1}^{n_0} D_j'(I_{p_j} - \bar{J}_{p_j})\mathbf{x}_j = \mathbf{z}, \qquad C_{p_j}'D_j\mathbf{1}_p = 0,$$

we have

$$\hat{\xi} = C_p(V-M)^{+}(I_p - \bar{J}_p)\sum_{j=1}^{n_0} D_j'(I_{p_j} - \bar{J}_{p_j})\mathbf{x}_j = C_p(V-M)^{+}\mathbf{z} = C_p\hat{\eta},$$

$$B_j\hat{\xi} = C_{p_j}D_j(I_p - \bar{J}_p)\hat{\eta} = C_{p_j}D_j\hat{\eta},$$

and

$$\hat{\sigma}_{\varepsilon}^{2} = \sum_{j=1}^{n_0} (\mathbf{x}_j - D_j\hat{\eta})'(I_{p_j} - \bar{J}_{p_j})(\mathbf{x}_j - D_j\hat{\eta})/f.$$

Note that $D_j\hat{\boldsymbol{\eta}} = (\hat{\eta}_{j_1}, \ldots, \hat{\eta}_{j_{p_j}})'$. The proof of (12) is complete. □

References

[1] R.P. Bhargava, M.S. Srivastava, On Tukey's confidence intervals for the contrasts in the means of the intraclass correlation model, J. Roy. Statist. Soc. B35 (1973) 147–152.
[2] P.J. Diggle, P. Heagerty, K.Y. Liang, S.L. Zeger, Analysis of Longitudinal Data, Oxford University Press, New York, 2002.
[3] R.J Levine, J.C Hauth, L.B. Curet, B.M. Sibai, P.M. Catalano, C.D. Morris, R. DerSimonian, J.R. Esterlitz, E.G. Raymond, D.E. Bild, J.D. Clemens, J.A. Cutler, Trial of calcium to prevent preeclampsia, New Engl. J. Medicine 337 (1997) 69–76.
[4] R.J.A. Little, D.B. Rubin, Statistical analysis with missing data, second edition, Wiley, New York, 2002.
[5] S.R. Searle, G. Casella, C.E. McCulloch, Variance Components, Wiley, New York, 1992.
[6] T. Seo, M.S. Srivastava, Testing equality of means and simultaneous confidence intervals in repeated measures with missing data, Biometrical J. 42 (2000) 981–993.
[7] M.S. Srivastava, E.M. Carter, The maximum likelihood method for non-response in sample survey, Survey Methodology 12 (1986) 61–72.
[8] T.H. Szatroski, Necessary and sufficient conditions for explicit solutions in the multivariate normal estimation problem for patterned means and covariances, Ann. Statist. 8 (1980) 802–810.
[9] G. Verbeke, G. Molenberghs, Linear Mixed Models for Longitudinal Data, Springer, New York, 2000.
[10] S.G. Wang, S.C. Chow, Advanced Linear Models: Theory and Applications, Marcel Dekker, Inc, New York, 1994.